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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/571,515	09/07/2006	Keith Foster	MASQ127218	8062

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EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/571,515	FOSTER ET AL.	
	Examiner	Art Unit	
	SHERIDAN SWOPE	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-97* is/are pending in the application.

4a) Of the above claim(s) *59 and 76-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58 and 60-75* is/are rejected.

7)☒ Claim(s) *61,63,66 and 71* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 March 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0207*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of Invention I and sub-invention (A) in their response of May 30, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The elected invention is directed to a method of making a targeted conjugate comprising a clostridial neurotoxin, a protease domain, and a translocation domain, wherein the conjugate inhibits exocytic fusion. Claims 58-97 are pending. Claims 59 and 76-97 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 58 and 60-75 are hereby examined.

Priority

The priority date granted for the instant invention is September 11, 2003, the filing date of UK 0321344.4, which disclosed the elected invention.

Title

The title is objected to because it is not descriptive of the elected invention, which is a method.

Drawings-Objections

Figures 4-7 are objected to because the lanes are not labeled or clearly described.

Abstract

The abstract is objected to because there are two versions; it is unclear which version is to be used. In addition, both abstracts appear to be too long.

MPEP 608.01(b) states

> The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

Specification-Objections

The specification is objected to for improper formatting. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Claims-Objections

Claims 61 and 63 are objected to for reciting non-elected subject matter. Claims 61 and 63 each recite a conjugate comprising a DNA sequence; such conjugates are encompassed by Invention II, not the elected invention.

For Claim 66, line 3, "RIA techniques, or radio-tracer techniques" should be corrected to "RIA techniques or radio-tracer techniques".

Claim 71 is objected to for being redundant with Claim 69. For purposes of examination, it is assumed that Claim 71 is meant to be dependent from Claim 70.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Double Patenting

> The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
>
> A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).
>
> An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Claims 58, 60-63, 74, and 75 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 33 of US Application

11/791,979. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 58, 60-63, 74, and 75 herein and Claim 33 of 11/791,979 are both directed to methods for making a conjugate comprising any targeting agonist any non-toxic proteases, and any translocation domain, wherein the conjugate inhibits exocytic fusion. The claims differ in that Claim 33 of 11/791,979 recites the limitation of methods for making a conjugate that inhibits exocytic fusion in a nociceptive sensory afferent cell, while Claims 58, 60-63, 74, and 75 herein do not recite said limitation. The portion of the specification in 11/791,979 that supports the recited methods includes embodiments that would anticipate Claims 58, 60-63, 74, and 75 herein, e.g., methods for making a conjugate comprising any targeting agonist any non-toxic proteases, and any translocation domain, wherein the conjugate inhibits exocytic fusion, which are also the methods specifically recited in Claim 33 of 11/791,979. Claims 58, 60-63, 74, and 75 herein cannot be considered patentably distinct over Claim 33 of 11/791,979 when there are specifically recited embodiments (methods for making a conjugate comprising any targeting agonist any non-toxic proteases, and any translocation domain, wherein the conjugate inhibits exocytic fusion) that would anticipate Claims 58, 60-63, 74, and 75 herein. Alternatively, Claims 58, 60-63, 74, and 75 herein cannot be considered patentably distinct over Claim 33 of 11/791,979 when there are specifically disclosed embodiments in 11/791,979 that supports Claim 33 of that application and falls within the scope of Claims 58, 60-63, 74, and 75 herein, because it would have been obvious to a skilled artisan to modify the methods of Claim 33 of 11/791,979 by selecting a specifically disclosed embodiment that supports that claims, i.e., methods for making a conjugate comprising any targeting agonist any non-toxic proteases, and any translocation domain, wherein the conjugate inhibits exocytic fusion, as disclosed in

11/791,979. One having ordinary skill in the art would have been motivated to do this, because such an embodiment is disclosed as being a preferred embodiment within Claim 33 of the other application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 58 and 60-75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

For Claim 58, the phrase "A method of designing" renders the claim indefinite. It is unclear whether said phrase means a method of making/producing or a method of thinking about how to make/produce the conjugate. The skilled artisan would not know the metes and bounds of the recited invention. Claims 60-73, as dependent from Claim 58, are indefinite for the same reason. For purposes of examination, it is assumed that the phrase "A method of designing" means "A method of making". It is noted that a method of thinking about how to make/produce a product would not be patentable subject matter under 35 U.S.C. 101.

For Claim 60, the phrase "suitable for re-targeting" renders the claim indefinite. It is unclear whether the agonist has the same targeting activity as the agonist in Claim 58 or a different, "re-targeting", activity. It is also unclear how to access whether any agonist is "suitable". The skilled artisan would not know the metes and bounds of the recited invention.

Claims 61-73, as dependent from Claim 60, are indefinite for the same reason. For purposes of examination, it is assumed that the agonist of Claim 60 has the same targeting activity as the agonist in Claim 58.

Claims 61 and 63 are indefinite for failing to be encompassed by the claim from which they depend, Claim 58. Claims 61 and 63 each recite a conjugate comprising a DNA sequence; such conjugates are not encompassed by Claim 58, which recites a conjugate comprising protein domains only.

For Claim 61, line 4, the phrase "an agent of the present invention" renders the claim indefinite. The skilled artisan would not know the metes and bounds of the recited invention.

It is unclear whether Claim 73 is meant to be dependent from Claim 67 or 72. For purposes of examination, it is assumed that Claim 73 is meant to be dependent from Claim 72.

Claims 60-75 are rendered indefinite for improper antecedent usage as follows.

For each of Claims 60-75, the phrase "A method according to Claim…" should be corrected to "The method according to Claim…".

For Claim 60, lines 7 & 8, "said molecule" lacks antecedent basis.

For Claims 61-63, line 1 each, "the step of" lacks antecedent basis.

For Claim 61, line 2-3, the phrase "a non-cytotoxic protease" should be corrected to "the non-cytotoxic protease".

For Claim 63, last line, the phrase "a target cell" should be corrected to "the target cell".

For Claim 64, line 2, Claim 67, line 3, Claim 68, line 3, Claim 70, line 3, and Claim 72, line 4, the term "agonist" should be corrected to "the agonist".

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 58 and 60-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a conjugate comprising the IL-13 targeting agonist and the catalytic and translocation domains of IgA protease, does not reasonably provide enablement for methods for making any conjugate comprising any targeting agonist, any non-toxic protease, and any translocation domain, wherein the conjugate inhibits exocytic fusion of any vesicle in any cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In regards to this enablement rejection, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill

of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 58 and 60-74 are so broad as to encompass any method for making any conjugate comprising any targeting agonist, any non-toxic protease, and any translocation domain, wherein the conjugate inhibits exocytic fusion of any vesicle in any cell. Claim 75 is so broad as to encompass any method for making any conjugate comprising any targeting agonist, any non-toxic clostridial neurotoxin protease, and any translocation domain, wherein the conjugate inhibits exocytic fusion of any vesicle in any cell. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods for making an extremely large number of conjugates, as broadly encompassed by the claims.

Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to making a conjugate comprising the IL-13 targeting agonist and the catalytic and translocation domains of IgA protease. It is noted that specification lists examples for making conjugates comprising fragments of clostridial neurotoxins; however, the structures/identities of said fragments have not been disclosed.

While recombinant and mutagenesis techniques as well as methods for assessing exocytosis are known, it is not routine in the art to make an essentially unlimited number of conjugates comprising any targeting agonist, any non-toxic protease, and any translocation domain and then screen said unlimited number of conjugates for inhibiting exocytic fusion of any vesicle in any cell. Furthermore, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable (Galye et al, 1993; Whisstock et al, 2003). In addition, one skilled in the art would expect any tolerance to modification for a given conjugate to diminish with each further and additional modification.

The specification does not support the broad scope of Claims 58 and 60-74, which encompasses all methods for making any conjugate comprising any targeting agonist, any non-toxic protease, and any translocation domain, wherein the conjugate inhibits exocytic fusion of any vesicle in any cell. The specification does not support the broad scope of Claim 75, which encompasses all methods for making any conjugate comprising any targeting agonist, any non-toxic clostridial neurotoxin protease, and any translocation domain, wherein the conjugate inhibits exocytic fusion of any vesicle in any cell. The specification does not support the broad scope of Claims 58 and 60-75 because the specification does not establish: (A) which targeting agonist, non-toxic protease, and translocation domains can be successfully used to inhibit exocytic fusion of any vesicle in any cell; (B) regions of the conjugate structure which may, or may not, be modified without affecting the desired activity; (C) the general tolerance of the desired activity to conjugate modification and extent of such tolerance; (D) a rational and

predictable scheme for making any conjugate comprising any targeting agonist, any non-toxic protease, and any translocation domain, wherein the conjugate inhibits exocytic fusion of any vesicle in any cell; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices of conjugates is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of methods for making any conjugate comprising any targeting agonist, any non-toxic protease, and any translocation domain, wherein the conjugate inhibits exocytic fusion of any vesicle in any cell. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Written Description

Claims 58 and 60-75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of methods for making any conjugate comprising any targeting agonist, any non-toxic protease, and any translocation domain, wherein the conjugate inhibits exocytic fusion of any vesicle in any cell. The specification teaches only a single representative species of such methods. Moreover, the

specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a method for making any conjugate comprising any targeting agonist, any non-toxic protease, and any translocation domain, wherein the conjugate inhibits exocytic fusion of any vesicle in any cell. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 58, 60, 62, 64, 74, and 75 are rejected under 35 U.S.C. 102(a,e) as being anticipated by Bigalke et al, 2004 (IDS; pub date 27-MAR-2003; filing date 27-AUG-2002). Bigalke et al teaches a method for identifying a targeting agonist, IgE, that increases exocytosis from mast cells (col 1, parg 3), preparing an agent comprising said targeting agonist linked to a domain comprising the catalytic and translocation domains of a clostridial neurotoxin (col 3, pargs 2 & 5). Therefore, Claims 58, 60, 62, 64, 74, and 75 are rejected under 35 U.S.C. 102(a,e) as being anticipated by Bigalke et al, 2004.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 58, 60-65, 67-69, and 72-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bigalke et al, 2004 in view of Skeberdis et al, 2001. The teachings of Bigalke et al are described above. Bigalke et al do not teach a method for identifying a targeting agonist that increases exocytosis, and preparing an agent comprising said targeting agonist linked to a domain comprising the catalytic and translocation domains of a clostridial neurotoxin, wherein exocytosis is detected by assaying the expression of a membrane channel at the plasma membrane. Skeberdis et al teach that insulin increases plasma membrane expression of NMDA receptor channels via exocytosis and this exocytosis is inhibited by a clostridium toxin (Fig 2-4 & 6). It would have been obvious to a person of ordinary skill in the art to modify the method of Bigalke et al to prepare a conjugate comprising the targeting agonist insulin linked to a domain comprising the catalytic and translocation domains of a clostridial neurotoxin, wherein exocytosis of the NMDA receptor channel is detected by assaying the expression of the receptor/channel at the plasma membrane, as taught by Skeberdis et al (Fig 6). Motivation to do so is derived from the desire to develop an agent useful for modulating the number of synaptic NMDA receptor channels, which are involved in processes including memory and learning. The expectation of success is high, as methods for making fusion proteins are well known in the art and Skeberdis et al demonstrates that the clostridial neurotoxin botulinum is effective at

inhibiting insulin-stimulated exocytosis of NMDA receptor channels. Therefore, Claims 67-69, 72, and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bigalke et al, 2004 in view of Skeberdis et al, 2001.

Claims 58, 60-65, 67, 70, 71, 74, and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bigalke et al, 2004 in view of Foran et al, 1999. The teachings of Bigalke et al are described above. Bigalke et al do not teach a method for identifying a targeting agonist that increases exocytosis, and preparing an agent comprising said targeting agonist linked to a domain comprising the catalytic and translocation domains of a clostridial neurotoxin, wherein exocytosis is detected by assaying the expression of a transporter at the plasma membrane. Foran et al teach that insulin increases plasma membrane expression of the GLUT4 transporter via exocytosis and this exocytosis is inhibited by a clostridium toxin (Fig 6). It would have been obvious to a person of ordinary skill in the art to modify the method of Bigalke et al to prepare an agent comprising the targeting agonist insulin linked to a domain comprising the catalytic and translocation domains of a clostridial neurotoxin, wherein exocytosis of the GLUT4 transporter is detected by assaying the expression of the transporter at the plasma membrane, as taught by Foran et al (Fig 5-6). Motivation to do so is derived from the desire to develop an agent useful for modulating the number of plasma membrane GLUT4 transporters, which is involved in glucose uptake. The expectation of success is high, as methods for making fusion proteins are well known in the art and Foran et al demonstrate that the clostridial neurotoxin botulinum is effective at inhibiting insulin-stimulated exocytosis of GLUT4 transporters. Therefore, Claims 70 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bigalke et al, 2004 in view of Foran et al, 1999.

Claim 66 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bigalke et al, 2004 in view of Yoshimaru et al, 2002. The teachings of Bigalke et al are described above. Bigalke et al do not teach a method for identifying a targeting agonist that increases exocytosis, and preparing an agent comprising said targeting agonist linked to a domain comprising the catalytic and translocation domains of a clostridial neurotoxin, wherein exocytosis is detected by assaying secretion using ELISA. Yoshimaru et al teach a method for measuring histamine secretion using ELISA (pg 614, parg 2). It would have been obvious to a person of ordinary skill in the art to modify the method of Bigalke et al to prepare an agent comprising the targeting agonist IgE linked to a domain comprising the catalytic and translocation domains of a clostridial neurotoxin, wherein exocytosis of histamine is detected by ELIZA. Motivation to do so is derived from the desire to develop an agent useful for modulating histamine release, which is involved in inflammation. The expectation of success is high, as methods for making fusion proteins are well known in the art and Yoshimaru et al teach a method for detecting exocytosis of histamine by ELIZA. Therefore, Claim 66 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bigalke et al, 2004 in view of Yoshimaru et al, 2002.

Allowable Subject Matter

No claims are allowable.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate

pages. It is also requested that the serial number of the application and date of amendment be referenced on every page of the reponse.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashed can be reached on 571-272-092834. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHERIDAN SWOPE/
Primary Examiner, Art Unit 1652